Effects of Rolipram and Cilostamide on Renal Functions and Cyclic AMP Release in Anesthetized Dogs[1]

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ABSTRACT

The present study was undertaken to examine whether phosphodiesterases III and IV regulate renal cAMP level and whether inhibition of these enzymes influences renal functions in anesthetized dogs. The intrarenal arterial infusion of rolipram (0.1, 0.3, and 1 μg/kg/min), a selective phosphodiesterase IV inhibitor, increased renal blood flow, glomerular filtration rate, urine flow rate, and urinary Na^+ excretion with elevating arterial and renal venous plasma cAMP concentrations and urinary cAMP excretion. However, cilostamide (0.1, 0.3, and 1 μg/kg/min), a selective phosphodiesterase III inhibitor, did not affect the values of these parameters. Indomethacin (3 mg/kg i.v. bolus and 1 mg/kg/min i.v. infusion), a cyclooxygenase inhibitor, reduced the basal arterial and renal venous plasma cAMP concentrations and blunted the rolipram-induced elevation of cAMP concentrations and urinary cAMP excretion. The effects of rolipram on renal hemodynamics and urine formation were attenuated in the presence of indomethacin. These results suggest that in the dog kidney in vivo, 1) phosphodiesterase IV, but not phosphodiesterase III, participates in degradation of cAMP and 2) the inhibition of phosphodiesterase IV enhances glomerular filtration and urinary Na^+ excretion, the responses of which depend in part on indomethacin-susceptible (prostaglandin-mediated, probably) control of basal cAMP level.

cAMP has been suggested to participate in the control of renal functions. It is well known that cAMP derivatives increase renal blood flow (Higashio et al., 1980), enhance glomerular filtration (Okahara et al., 1977), and cause diuresis (Robinson and Mirkovitch, 1980).

Intracellular cAMP level is regulated by phosphodiesterase (PDE). PDEs have been classified into at least seven isozyme families (Beavo and Reifsnyder, 1990; Nicholson et al., 1991; Beavo, 1995), among which PDE III (cGMP-inhibited PDE) and PDE IV (cAMP-specific PDE) preferentially hydrolyze cAMP rather than cGMP (Thompson, 1991) and have high affinity for cAMP. PDE III has been identified in smooth muscles (Reinhart et al., 1995), platelets (Hidaka et al., 1979), and cardiac tissues (Lindgren and Andersson, 1991), and PDE IV has been identified in brain (Beavo, 1995) and tracheal tissues (Torphy et al., 1992). The kidney is suggested to contain both PDE III and IV (Lindgren and Andersson, 1991).

Inhibitors of these cAMP-specific PDEs are useful pharmacological tools to evaluate the physiological role of cAMP. The i.v. infusion of lixazone, a PDE III inhibitor, or rolipram, a PDE IV inhibitor, suppresses development of mesangial pro-

liferative glomerulonephritis (Tsuboi et al., 1996), and Ro 20-1724, a PDE IV inhibitor, attenuates the endotoxin-induced acute renal failure (Begany et al., 1996) in rats. These observations suggest that elevation of renal cAMP level by inhibition of its degradation can improve renal functions.

However, there has been little information on the contribution of PDE III and IV to regulation of renal cAMP level and the influence by the inhibition of these PDEs on renal functions in nonpathophysiological conditions. To access this issue, in the present study we examined the effects of cilostamide (selective PDE III inhibitor) (Hidaka et al., 1979) and rolipram (selective PDE IV inhibitor) (Disanto and Heaslip, 1995) on renal cAMP release and renal functions in anesthetized dogs.

Materials and Methods

Animal Preparation. All animal protocols were reviewed and approved by the Animal Subjects Committee of Pharmaceutical Institute, Tohoku University. Mongrel dogs of either sex weighing 8 to 18 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and then intubated and artificially ventilated with room air. The cephalic veins were cannulated for drug administration. Decamethonium bromide (0.25 mg/kg i.v.) was administered to prevent spontaneous active respiratory movement. Anesthesia was maintained by a continuous i.v. infusion of sodium pentobarbital at a rate of 5 mg/kg/h throughout the experiments. Inulin, dissolved in 0.45% NaCl and 2.5% dextrose, was given i.v. at a prime dose of 50 mg/kg and at

ABBREVIATIONS: PDE, phosphodiesterase; DMSO, dimethyl sulfoxide.

a maintenance dose of 1 mg/kg/min (0.1 ml/kg/min). The right brachial artery was cannulated for collection of arterial blood samples and measurement of mean arterial pressure with a pressure transducer (MPU-0.5; Nihon Kohden, Tokyo, Japan) and of heart rate with a cardiotachometer (RT-5; Nihon Kohden). The right and left kidneys were exposed by retroperitoneal flank incisions. Catheters for urine collection were inserted into both the right and left ureters. Curved 18-gauge needles connected to silicone tubes were inserted into the right and left renal veins to collect renal venous blood samples. All visible renal nerves were dissected away from the renal vessels and cut after ligation. Electromagnetic flow probes (2.5–3.5 mm in diameter; Nihon Kohden) were attached at the right and left renal arteries to measure renal blood flow with square-wave flowmeters (MF-27; Nihon Kohden). Curved 25-gauge needles connected to polyethylene tubes were inserted into both the right and left renal arteries for drug infusion. Mean arterial pressure, heart rate, and renal blood flow were recorded with a polygraph system (RM-6000, Nihon Kohden).

Experimental Protocol. After the completion of surgery, more than 90 min was allowed for stabilization. When renal blood flow and urine flow rate reached constant levels for more than three consecutive monitoring periods (10 min each), urine and blood samples for basal values were obtained. Urine was collected over a 10-min period, and arterial and renal venous blood samples were withdrawn simultaneously at the midpoint of urine collection.

In group 1 ($n = 5$), 0.5% dimethyl sulfoxide (DMSO) (vehicle for rolipram and cilostamide) was infused into the right or left renal artery (0.2 ml/min) for 60 min. Beginning at 10, 30, and 50 min after the start of infusion, the urine and blood sampling was performed. In groups 2 and 3, cilostamide (group 2, $n = 7$) or rolipram (group 3, $n = 7$) was infused into the renal artery at increasing rates of 0.1, 0.3, and 1 μg/kg/min for 20 min each. Beginning at 10 min after the start of infusion at each dose, the 10-min urine collection and blood sampling were performed. In group 4 ($n = 8$), the rolipram infusion and the urine and blood samplings were performed in a similar manner as in group 2 in the presence of indomethacin. Indomethacin was bolus injected (3 mg/kg i.v.) 30 min before the start of experiments and then continuously infused (1 mg/kg/h i.v.) throughout the experiments.

Measurement. Blood samples were transferred into chilled tubes containing diammonium EDTA (5–10 mg/ml blood) and then centrifuged to obtain plasma samples. Glomerular filtration rate was determined as inulin clearance (Davidson and Sackner, 1963). Inulin concentration in plasma and urine was measured by the anthrone method. Na^+ and K^+ were measured by flame photometry (775A; Hitachi). Plasma osmolarity and urine osmolarity were measured by the freezing point depression method (OM801; Vogel). Plasma and urinary cAMP concentrations were measured by radioimmunoassay kit (Diagnostics Division, Yamasa Corp., Tokyo, Japan).

Drugs. Cilostamide (Otsuka Pharmaceutical Company, Osaka, Japan) and rolipram (Meiji Seika Kaisha, Ltd., Tokyo, Japan) were dissolved in a small amount of DMSO and diluted with 0.9% saline (the final concentration of DMSO was less than 0.5%). Indomethacin (Sigma Chemical Co., St. Louis, MO) was dissolved in 1 mM Na_2CO_3 and diluted with 0.9% saline. This solution was neutralized (pH 7.5–8.5) with HCl.

Data Analysis. All values are expressed as mean ± S.E. The kidneys were removed out at the end of experiments and weighed after decapsulation. Renal blood flow and urine flow rate and parameters derived from them are expressed as per kidney weight (g). Data for urine formation were transformed to logarithms to obtain normal distribution before the application of statistical procedures. Overall, statistical differences were evaluated by ANOVA. Statistical differences of basal values versus drug infusion were evaluated by Dunnett's test, and those of rolipram versus rolipram plus indomethacin were evaluated by simple main effects. Differences at $p < .05$ were considered to be statistically significant.

Results

Vehicle for rolipram and cilostamide (0.5% DMSO) infused into the renal artery at 0.2 ml/min for 60 min did not cause a statistically significant change in systemic or renal hemodynamics or urine formation (group 1, Table 1).

Intrarenal arterial infusion of cilostamide (0.1, 0.3, and 1 μg/kg/min) did not affect renal hemodynamics or urine formation (group 2, Table 2 and Fig. 1), except that cilostamide at 1 μg/kg/min lowered mean arterial pressure and renal vascular resistance (Table 2). The change in renal vascular resistance was also observed in the contralateral noninfused kidney (data not shown).

Intrarenal arterial infusion of rolipram (0.1, 0.3, and 1 μg/kg/min) increased renal blood flow and decreased renal vascular resistance in a dose-dependent manner (group 3, Fig. 2 and Table 3). Rolipram at the highest dose (1 μg/kg/min) lowered mean arterial pressure and increased heart rate (Table 3). Rolipram at 0.1 and 0.3 μg/kg/min increased glomerular filtration rate, urine flow rate, urinary Na^+ excretion, osmolar clearance, and free water reabsorption, but rolipram at 1 μg/kg/min reduced glomerular filtration rate, urine flow rate, urinary Na^+ excretion, and osmolar clearance from their increased levels (Table 3 and Fig. 2). There was no change in urine osmolarity (Table 3). Filtration fraction and fractional Na^+ excretion tended to be increased by

TABLE 1
Effects of vehicle (0.5% DMSO) on systemic and renal hemodynamics and urine formation (group 1)

	Basal	0.5% DMSO		
		10–20 min	30–40 min	50–60 min
MAP (mm Hg)	105 ± 6	103 ± 7	103 ± 7	102 ± 7
HR (beats/min)	120 ± 10	119 ± 10	118 ± 10	117 ± 10
RBF (ml/min/g)	4.6 ± 0.2	4.4 ± 0.2	4.3 ± 0.2	4.4 ± 0.3
RVR (mm Hg/ml/min/g)	23 ± 1	23 ± 2	24 ± 2	24 ± 3
GFR (ml/min/g)	0.7 ± 0.1	0.7 ± 0.0	0.6 ± 0.1	0.6 ± 0.1
FF (%)	29 ± 4	31 ± 4	28 ± 5	28 ± 8
UV (μl/min/g)	4.3 ± 1.1	4.4 ± 1.3	4.9 ± 1.5	4.3 ± 1.5
UNaV (μEq/min/g)	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
FENa (%)	0.9 ± 0.2	0.7 ± 0.2	0.8 ± 0.3	0.7 ± 0.2
Uosm (Osm/kg H_2O)	1.4 ± 0.2	1.3 ± 0.2	1.3 ± 0.3	1.3 ± 0.3
Cosm (μl/min/g)	18 ± 3	18 ± 3	17 ± 3	14 ± 4
T^CH_2O (μl/min/g)	14 ± 2	13 ± 2	12 ± 1	9 ± 2

Values are mean ± S.E. ($n = 5$). MAP, mean arterial pressure; HR, heart rate; RBF, renal blood flow; RVR, renal vascular resistance; GFR, glomerular filtration rate; FF, filtration fraction; UV, urine flow rate; UNaV, urinary Na^+ excretion; FENa, fractional Na^+ excretion; Uosm, urine osmolarity; Cosm, osmolar clearance; T^CH_2O, free water reabsorption. 0.5% DMSO was infused into renal artery at a rate of 0.2 ml/min. There were no statistically significant differences between values before DMSO infusion (basal) and values during DMSO infusion.

TABLE 2
Effects of cilostamide on systemic and renal hemodynamics and urine formation (group 2)

	Basal	Cilostamide (μg/kg/min)		
		0.1	0.3	1
MAP (mm Hg)	110 ± 7	109 ± 8	106 ± 9	100 ± 9*
HR (beats/min)	110 ± 8	109 ± 8	111 ± 7	115 ± 7
RVR (mm Hg/ml/min/g)	34 ± 4	33 ± 4	32 ± 4	29 ± 4**
FF (%)	27 ± 3	27 ± 4	28 ± 4	27 ± 4
FENa (%)	1.6 ± 0.6	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.3
Uosm (Osm/kg H_2O)	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.1	0.9 ± 0.2
Cosm (μl/min/g)	15 ± 2	14 ± 2	16 ± 3	15 ± 3
$T^C H_2O$ (μl/min/g)	10 ± 2	8 ± 2	10 ± 2	9 ± 2

Values are mean ± S.E. ($n = 7$). MAP, mean arterial pressure; HR, heart rate; RVR, renal vascular resistance; FF, filtration fraction; FENa, fractional Na^+ excretion; Uosm, urine osmolarity; Cosm, osmolar clearance; $T^C H_2O$, free water reabsorption. Cilostamide was infused into renal artery at increasing doses (0.1, 0.3, and 1 μg/kg/min). * $P < .05$, ** $P < .01$ compared with corresponding basal value.
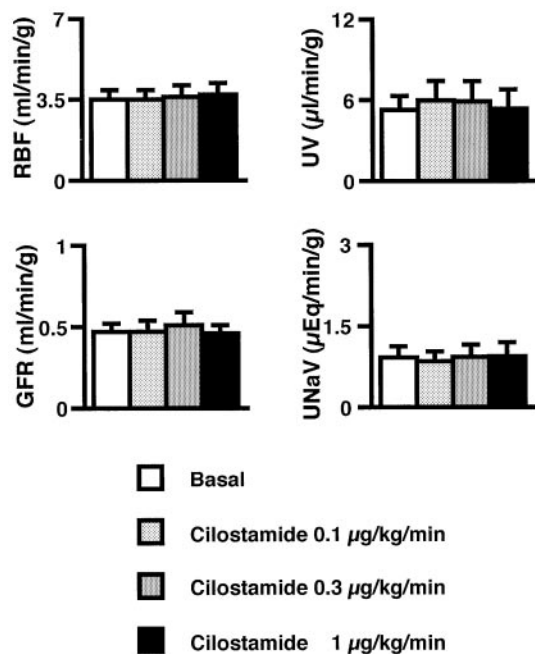

Fig. 1. Effects of cilostamide on renal hemodynamics and urine formation (group 2). RBF, renal blood flow; GFR, glomerular filtration rate; UV, urine flow rate; UNaV, urinary Na^+ excretion. Values are mean ± S.E. ($n = 7$). Cilostamide was infused into the renal artery at the increasing doses (0.1, 0.3, and 1 μg/kg/min). There were no statistically significant differences between the basal values and the values during cilostamide infusion.
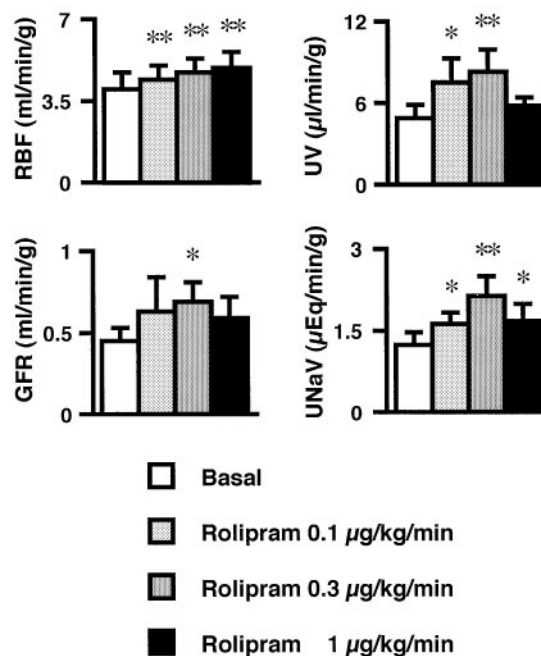

Fig. 2. Effects of rolipram on renal hemodynamics and urine formation (group 3). RBF, renal blood flow; GFR, glomerular filtration rate; UV, urine flow rate; UNaV, urinary Na^+ excretion. Values are mean ± S.E. ($n = 7$). Rolipram was infused into the renal artery at increasing doses (0.1, 0.3, and 1 μg/kg/min). * $P < .05$, ** $P < .01$ compared with the corresponding basal value.

rolipram at 0.1 and 0.3 μg/kg/min (Table 3), although these changes were not statistically significant. The values of renal parameters in the contralateral noninfused kidney did not change throughout this experiment (data not shown).

Cilostamide did not affect arterial plasma cAMP concentration, renal venous plasma cAMP concentration, or urinary cAMP excretion (group 2, Fig. 3). In additional experiments, a higher dose of cilostamide (3 μg/kg/min) caused systemic hypotension but did not affect plasma cAMP concentration or urinary cAMP excretion (data not shown). This dose of cilostamide reduced urine flow rate and urinary Na^+ excretion (data not shown).

Rolipram increased arterial plasma cAMP concentration, renal venous plasma cAMP concentration, and urinary cAMP excretion in a dose-dependent manner (group 3, Fig. 3). The increases in renal venous plasma cAMP concentration from the level before rolipram infusion (51 ± 13%, 112 ± 30%, and 218 ± 56% during rolipram infusion at 0.1, 0.3, and 1.0

μg/kg/min, respectively) were significantly higher ($P < .05$) than the increases in arterial plasma cAMP concentration (14 ± 3%, 32 ± 6%, and 84 ± 7%).

Intravenous administration of indomethacin (group 4) reduced arterial plasma cAMP concentration from 8.8 ± 0.9 to 6.8 ± 0.6 pmol/ml ($P < .01$), renal venous plasma cAMP concentration from 6.9 ± 0.4 to 5.4 ± 0.4 pmol/ml ($P < .01$), and renal blood flow from 3.3 ± 0.4 to 3.1 ± 0.3 ml/min/g ($P < .05$). Other values after indomethacin treatment were glomerular filtration rate of 0.50 ± 0.08 ml/min/g, urine flow rate of 4.19 ± 1.17 μl/min/g, urinary Na^+ excretion of 0.96 ± 0.22 μEq/min/g, and urinary cAMP excretion of 8.5 ± 5.7 pmol/min/g; these were not statistically different from the values before indomethacin treatment. Urinary cAMP excretion increased after indomethacin treatment in one animal, whereas it decreased in other animals. As a result, no statis-

TABLE 3
Effects of rolipram on systemic and renal hemodynamics and urine formation (group 3)

	Basal	Rolipram (μg/kg/min)		
		0.1	0.3	1
MAP (mm Hg)	109 ± 6	107 ± 7	106 ± 7	103 ± 9*
HR (beats/min)	122 ± 16	126 ± 17	137 ± 18**	144 ± 19**
RVR (mm Hg/ml/min/g)	32 ± 5	27 ± 4**	25 ± 3**	23 ± 3**
FF (%)	21 ± 3	24 ± 5	29 ± 7	21 ± 4
FENa (%)	2.2 ± 0.5	2.8 ± 0.7	2.7 ± 0.6	2.3 ± 0.3
Uosm (Osm/kg H$_2$O)	1.1 ± 0.2	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1
Cosm (μl/min/g)	16 ± 1	20 ± 2*	23 ± 2**	20 ± 3*
T^{C}H$_2$O (μl/min/g)	11 ± 1	13 ± 2	15 ± 2*	15 ± 2

Values are mean ± S.E. (n = 7). MAP, mean arterial pressure; HR, heart rate; RVR, renal vascular resistance; FF, filtration fraction; FENa, fractional Na$^+$ excretion; Uosm, urine osmolarity; Cosm, osmolar clearance; T^{C}H$_2$O, free water reabsorption. Rolipram was infused into renal artery at increasing doses (0.1, 0.3, and 1 μg/kg/min). * $P < .05$, ** $P < .01$ compared with corresponding basal value.
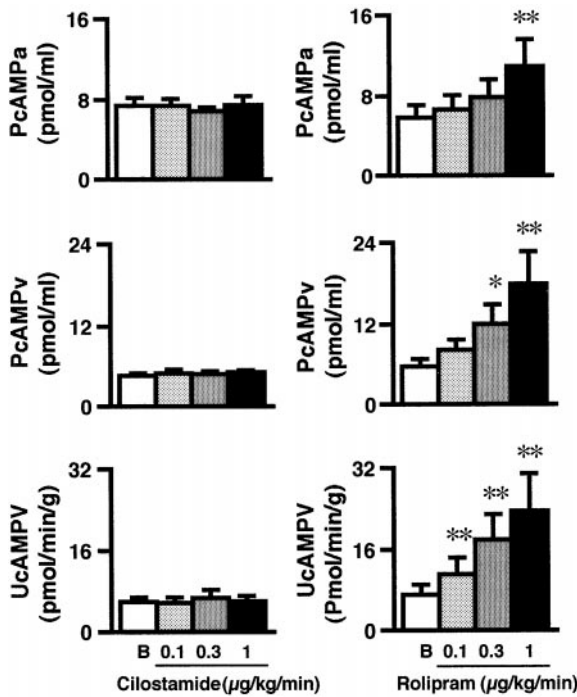

Fig. 3. Effects of cilostamide (group 2, n = 7) and rolipram (group 3, n = 7) on cAMP release. B, basal; PcAMPa, arterial plasma cAMP concentration; PcAMPv, renal venous plasma cAMP concentration; UcAMPV, urinary cAMP excretion. Values are mean ± S.E. Cilostamide or rolipram was infused into the renal artery at the increasing doses. *$P < .05$, **$P < .01$ compared with the corresponding basal value.

tically significant effect of indomethacin on this parameter was observed.

Figure 4 compares the rolipram-induced renal responses (percent changes from the levels before rolipram infusion) between nontreated dogs (group 2) and indomethacin-treated dogs (group 4). Indomethacin attenuated the increasing effects of rolipram on renal blood flow, glomerular filtration rate, urine flow rate, urinary Na$^+$ excretion, arterial and renal venous plasma cAMP concentrations, and urinary cAMP excretion. The values of renal parameters in the contralateral kidney remained unchanged throughout this experiment (data not shown).

Discussion

The aim of the present study was to clarify the roles of cAMP-specific PDEs (types III and IV) in regulation of renal cAMP level and the influence of their inhibition on renal
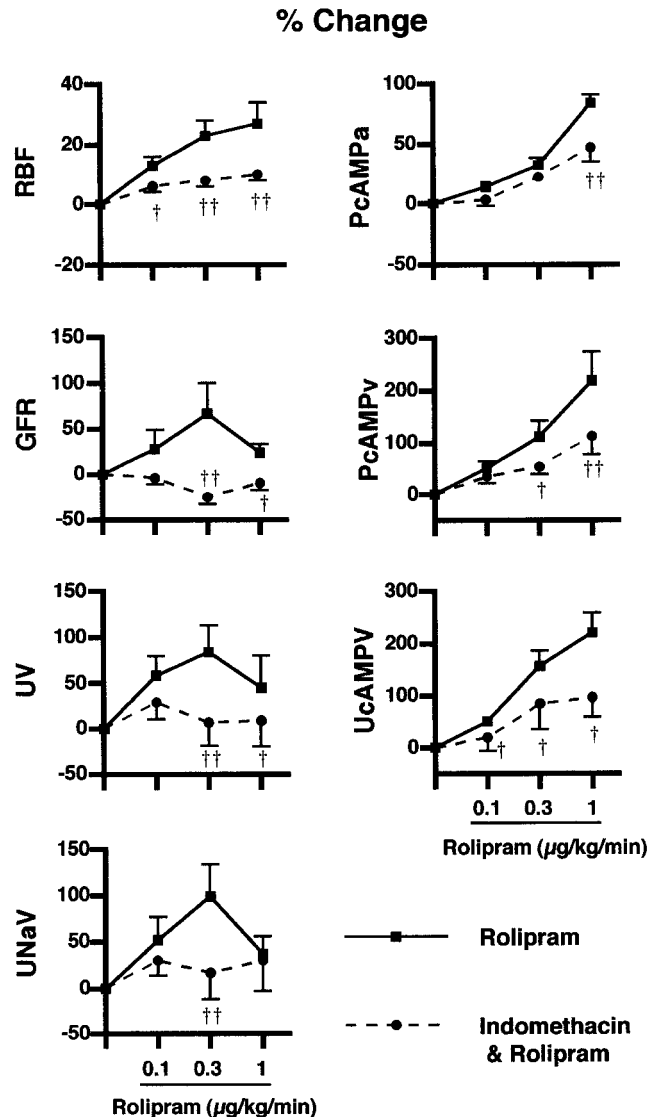

Fig. 4. Effects of rolipram on renal hemodynamics, urine formations, and cAMP release in the absence (group 3, n = 7) or presence (group 4, n = 8) of indomethacin (3 mg/kg and 1 mg/kg/h i.v.). Abbreviations are as in Figs. 1 and 2. Values (mean ± S.E.) represent percent changes from the basal levels. †$P < .05$, ††$P < .01$ compared with the values at corresponding sampling points in the nontreated animals (group 3).

functions in vivo. Cilostamide and rolipram, a selective PDE III inhibitor (Hidaka et al., 1979) and a selective PDE IV inhibitor (Disanto and Heaslip, 1995), respectively, were in-

fused into the renal artery of anesthetized dogs. These drugs are shown to have higher selectivity for each PDE than other inhibitors (Beavo and Reifsnyder, 1990; Thompson, 1991) and exert their actions on the renal tissues (Yamaki et al., 1992; Chini et al., 1994). We also confirmed that a vehicle for these inhibitors (0.5% DMSO) did not affect renal functions (group 1).

Cilostamide at increasing doses of 0.1, 0.3, and 1 μg/kg/min did not affect arterial or renal venous plasma cAMP concentration or urinary cAMP excretion (group 2). The values of parameters for glomerular function or urine formation did not change during the cilostamide infusion, whereas cilostamide at 1 μg/kg/min lowered systemic blood pressure and renal vascular resistance. The reduction in renal vascular resistance may be due to autoregulation of renal blood flow against the hypotension and may not be related to a renal action of cilostamide because this response was also observed in the contralateral noninfused kidney. The calculated concentrations of cilostamide in renal blood were 0.3 to 3 μM, the range of which was 6 to 60 times higher than its IC_{50} values (0.05 μM) obtained with human platelets (Hidaka and Endo, 1984). Therefore, the doses of cilostamide used in the present study seem to be sufficient to inhibit PDE III. Moreover, in additional experiments, the infusion of cilostamide even at 3 μg/kg/min failed to affect the renal cAMP release. It was reported that PDE III inhibitor did not cause vasodilation or cAMP release in the isolated perfused rat kidney (Jackson et al., 1997), and the activity of PDE III was much lower than that of PDE IV in the rat collecting duct cell (Yamaki et al., 1992). In agreement with these reports, the results of the present study suggest that PDE III plays little or no role in regulation of cAMP level in the dog kidney and that the inhibition of PDE III does not affect renal functions.

It should be noted, however, that PDE III inhibitors can suppress the development of mesangial proliferative glomerulonephritis in rats (Tsuboi et al., 1996) and that cilostamide attenuates the formation of reactive oxygen metabolite in rat glomeruli (Chini et al., 1994). The present study leaves open the possibility that PDE III participates in regulation of renal cAMP level in some pathophysiological conditions.

Rolipram at increasing doses of 0.1, 0.3, and 1 μg/kg/min (group 3) elevated arterial and renal venous plasma cAMP concentrations. The elevation of cAMP concentration in renal venous plasma was significantly higher than that in arterial plasma, and rolipram also increased urinary cAMP excretion. Rolipram may thus accumulate cAMP by inhibiting its degradation in the kidney, although we have no direct evidence that these parameters correctly reflect the change in cellular cAMP content. The kidney is known to have high PDE IV activity (Kariya and Dage, 1988; Masuoka et al., 1990). Our present study suggests that the cAMP level is predominantly regulated by PDE IV in the dog kidney in vivo.

The rolipram infusion increased renal blood flow and glomerular filtration rate. Filtration fraction remained unchanged or slightly increased during the rolipram infusion. It is therefore possible that rolipram, like as the adenylate cyclase activator forskolin (Tamaki et al., 1991), preferentially dilates the preglomerular rather than the postglomerular vessels. Although the inhibition of PDE IV might affect the filtration coefficient, the present result suggests that PDE IV degrades cAMP more preferentially at the preglomerular site in the renal vasculature. Rolipram also in-

creased urine flow rate and urinary Na^+ excretion, which may result from the enhanced glomerular filtration. It has been reported that cAMP inhibits Na^+,K^+-ATPase in the rat ascending limb of Henle's loop (Nishi et al., 1993), Na^+-H^+ antiport in the rabbit tubular brush-border membrane (Weinman et al., 1987), and sodium reabsorption in the dog kidney (Robinson and Mirkovitch, 1980). Because rolipram tended to elevate fractional Na^+ excretion in the present study, the rolipram-induced urinary responses may also involve the inhibition of PDE IV at the renal tubular site. Another PDE IV inhibitor (Ro 20-1724) is known to improve renal functions by counteracting the vasoconstriction and hypofiltration in the endotoxin-induced acute renal failure model (Begany et al., 1996). Our present study is the first to demonstrate the ability of the PDE IV inhibitor rolipram to enhance glomerular filtration and urine formation with increasing renal cAMP release under the more physiological condition.

The highest dose of rolipram (1 μg/kg/min) did not further increase glomerular filtration rate, urine flow rate, or urinary Na^+ excretion despite the dose-related increase in renal blood flow and elevation of renal venous plasma cAMP concentration. This dose of rolipram significantly lowered mean arterial pressure. It is likely that a reduction in renal perfusion pressure secondary to the systemic hypotension reduced glomerular filtration pressure and thereby inhibited the cAMP-mediated facilitation of glomerular filtration. This may counteract and mask the natriuretic property of rolipram at the hypotensive dose.

To elucidate the relationship between the renal actions of rolipram and the inhibition of renal cAMP degradation, we also examined whether a reduction in endogenous cAMP production affects the rolipram-induced changes in renal cAMP release and renal functions. Prostaglandins are well known to activate cAMP production (Oliw et al., 1977; Noland et al., 1992) and to participate in the control of renal vascular tone, mesangial and glomerular functions, and the handling of salt and water (Ando and Asano, 1995). It is therefore likely that the renal actions of rolipram involve the enhancement of prostaglandin-cAMP pathway. In this regard, we evaluated the rolipram-induced responses in the presence of indomethacin, a cyclooxygenase inhibitor (group 4). We had previously confirmed that indomethacin can effectively suppress prostaglandin production in the dog kidney (Hisa et al., 1984). The i.v. administration of indomethacin (3 mg/kg plus 1 mg/kg/h) lowered arterial and renal venous plasma cAMP concentrations in the basal state, suggesting that renal cAMP production is mediated in part by the prostaglandin system. In the indomethacin-treated group, the increases in renal venous cAMP concentration and urinary cAMP excretion during rolipram infusion at any doses were significantly smaller than the responses obtained in the nontreated group (group 3). The blunted cAMP release responses indicate the reduced degradation of cAMP by PDE IV under the lower basal cAMP level. Indomethacin also attenuated the rolipram-induced increases in renal blood flow, glomerular filtration rate, urine flow rate, and urinary Na^+ excretion. These results demonstrate that the renal actions of rolipram are closely related to changes in basal renal cAMP level and suggest that they are due to the inhibition of cAMP degradation.

However, other interpretation of the present results are

also possible because we did not confirm the specificity of either rolipram or indomethacin in the kidney. For example, rolipram might stimulate renal prostaglandin production and thereby elevate cAMP level to cause the renal actions, or indomethacin might facilitate cAMP degradation by acting on PDEs. We cannot rule out these possibilities.

In summary, the present study demonstrates that rolipram, but not cilostamide, can enhance glomerular filtration and urinary Na^+ and water excretion with increasing renal cAMP release and that indomethacin reduces basal renal cAMP release and attenuates the rolipram-induced cAMP release and renal responses in anesthetized dogs. PDE IV may be one of the major determinants of renal cAMP content and thereby play an important role in the regulation of renal functions. The renal responses induced by inhibition of PDE IV may depend in part on indomethacin-susceptible control mechanisms of basal cAMP level such as the prostaglandin-mediated cAMP production.

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